



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/55, 31/135	A1	(11) International Publication Number: WO 98/1189' (43) International Publication Date: 26 March 1998 (26.03.98)
(21) International Application Number: PCT/US97/15874 (22) International Filing Date: 9 September 1997 (09.09.97) (30) Priority Data: 60/026,884 23 September 1996 (23.09.96) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BYMASTER, Franklin, P. [US/US]; 8545 North 650 East, Brownsburg, IN 46112 (US). PERRY, Kenneth, W. [US/US]; 4460 Carson Avenue, Indianapolis, IN 46227 (US). TOLLEFSON, Gary, D. [US/US]; 9052 Diamond Pointe, Indianapolis, IN 46236 (US). (74) Agents: TITUS, Robert, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW) Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMBINATION THERAPY FOR TREATMENT OF PSYCHOSES (57) Abstract The invention provides antipsychotic methods and compositions.		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

-1-

COMBINATION THERAPY FOR TREATMENT OF PSYCHOSES

5 The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides antipsychotic methods and compositions.

Psychoses are serious mental illnesses characterized by defective or lost contact with reality. Psychotic patients may also suffer hallucinations and delusions as part of their disease. Psychoses exact a
10 tremendous emotional and economic toll on the patients, their families, and society as a whole. While the mechanisms underlying these diverse disease states are poorly understood, recently discovered therapies are offering new hope for the treatment of psychotic patients.
15 Progress in the treatment of psychotic conditions has been achieved through the introduction of new, atypical antipsychotic agents. While the side effect profile of these atypical antipsychotics is far superior to that of traditional agents, weight gain is a side effect that has
20 been observed in patients treated with the atypical antipsychotics.

These new agents, while holding the promise of improving the lives of psychotic patients immeasurably, may not be sufficient to treat every psychotic patient. Since
25 psychotic conditions appear to have a complex etiology, some schizophrenics which exhibit depressive episodes during the course of their illness, or depressed individuals which also have psychotic episodes, may not find total relief using only an atypical antipsychotic agent.

30 The invention provides a method for treating a patient suffering from or susceptible to psychosis, acute mania, mild anxiety states, or depression in combination with psychotic episodes, comprising administering to said patient an effective amount of a first component which is an
35 atypical antipsychotic, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

-2-

The invention also provides a pharmaceutical composition which comprises a first component which is an atypical antipsychotic, and a second component which is a serotonin reuptake inhibitor.

5 In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

10 The Compounds

In the general expressions of the present invention, the first component is a compound which acts as an atypical antipsychotic. The essential feature of an atypical antipsychotic is less acute extrapyramidal
15 symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of
20 overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations
25 associated with therapy (Beasley, et al., Neuropsychopharmacology, 14(2), 111-123, (1996)). Atypical antipsychotics include, but are not limited to:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound
30 and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety;

35 Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Patent No. 3,539,573, which is herein incorporated by reference in

-3-

its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., **24**, 62 (1988));

5 Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663, which is herein incorporated by reference in its entirety;

10 Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 15 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety;

 Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl)-1-piperazinyl]ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia 20 are described in U.S. Patent No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; and

 Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. 25 Patent No. 4,831,031. U.S. Patent Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety.

 Similarly, when the invention is regarded in its broadest sense, the second component compound is a compound 35 which functions as a serotonin reuptake inhibitor. The measurement of a compound's activity in that utility is now a standard pharmacological assay. Wong, et al.,

-4-

Neuropsychopharmacology 8, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described by Wong *supra*. Serotonin reuptake inhibitors include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., J. Med. Chem. 31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers;

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent;

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., Neuropharmacology 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

-5-

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., Eur. J. Pharmacol. 41, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., Int. Clin. Psychopharmacol. 2, 225 (1987), and Timmerman et al., ibid., 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen et al., Brit. J. Pharmacol. 60, 505 (1977); and De Wilde et al., J. Affective Disord. 4, 249 (1982); and Benfield et al., Drugs 32, 313 (1986);

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, Eur. J. Pharmacol. 47, 351 (1978); Hassan et al., Brit. J. Clin. Pharmacol. 19, 705 (1985); Laursen et al., Acta Psychiat. Scand. 71, 249 (1985); and Battegay et al., Neuropsychobiology 13, 31 (1985); and

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Patent 4,536,518.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

It will be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single serotonin reuptake inhibitor as a second component compound is preferred, combinations of two or more serotonin reuptake inhibitors may be used as a second component if necessary or desired.

-6-

While all combinations of first and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

5 olanzapine/fluoxetine
 olanzapine/venlafaxine
 olanzapine/citalopram
 olanzapine/fluvoxamine
 olanzapine/paroxetine
10 olanzapine/sertraline
 olanzapine/milnacipran
 olanzapine/duloxetine
 clozapine/fluoxetine
 risperidone/fluoxetine
15 sertindole/fluoxetine
 quetiapine/fluoxetine
 ziprasidone/fluoxetine

20 In general, combinations and methods of treatment using olanzapine as the first component are preferred. Furthermore, combinations and methods of treatment using fluoxetine as the second component are preferred. Especially preferred are combinations and methods of treatment using olanzapine as the first component and
25 fluoxetine as the second component.

 It is especially preferred that when the first component is olanzapine, it will be the Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

30

d

10.2689

8.577

7.4721

7.125

6.1459

-7-

d

6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

5 A typical example of an x-ray diffraction pattern
for Form II is as follows wherein d represents the
interplanar spacing and I/I₁ represents the typical relative
intensities:

-8-

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer

-9-

having a copper $K\alpha$ radiation source of wavelength, λ
=1.541Å.

5 It is further preferred that the Form II
olanzapine polymorph will be administered as the
substantially pure Form II olanzapine polymorph.

As used herein "substantially pure" refers to Form
II associated with less than about 5% Form I, preferably
less than about 2% Form I, and more preferably less than
about 1% Form I. Further, "substantially pure" Form II will
10 contain less than about 0.5% related substances, wherein
"related substances" refers to undesired chemical impurities
or residual solvent or water. In particular, "substantially
pure" Form II should contain less than about 0.05% content
of acetonitrile, more preferably, less than about 0.005%
15 content of acetonitrile. Additionally, the polymorph of the
invention should contain less than 0.5% of associated water.

The polymorph obtainable by the process taught in
the '382 patent will be designated as Form I and has a
typical x-ray powder diffraction pattern substantially as
20 follows, obtained using a Siemens D5000 x-ray powder
diffractometer, wherein d represents the interplanar
spacing:

d

9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255

-10-

d

4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I₁ represents the typical relative intensities:

5

d	I/I₁
9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
6.2439	5.21
5.5895	1.10

-11-

d	I/I ₁
5.3055	0.95
4.9815	6.14
4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40
2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10
2.5956	1.73

5 The x-ray powder diffraction patterns herein were obtained with a copper K α of wavelength $\lambda = 1.541\text{\AA}$. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I₁".

Though Form II olanzapine is preferred it will be understood that as used herein, the term "olanzapine"

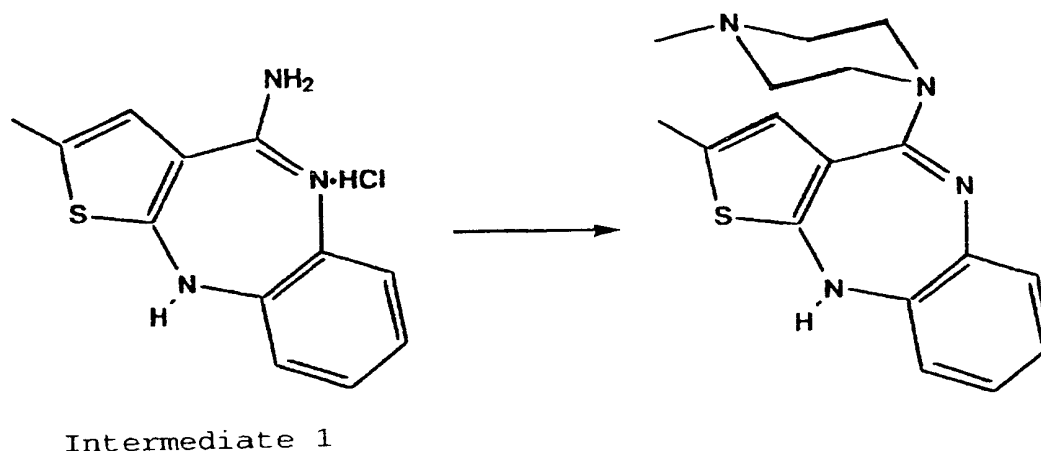
-12-

embraces all solvate and polymorphic forms unless specifically indicated.

Preparation 1

Technical Grade olanzapine

5



10 In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes

Intermediate 1 : 75 g

N-Methylpiperazine (reagent) : 6 equivalents

15 Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

20 A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until \approx 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and

25

-13-

the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L). The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency \geq 97%, total related substances < 0.5% and an isolated yield of > 73%.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

-14-

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

-15-

Administration

5 The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

15 Olanzapine: from about 0.25 to 50 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;

 Clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;

20 Risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;

 Sertindole: from about .0001 to 1.0 mg/kg daily;

 Quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;

25 Ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;

 Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;

30 Duloxetine: from about 1 to about 30 mg once/day; preferred, from about 5 to about 20 mg once/day;

 Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;

35 Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;

-16-

Citalopram: from about 5 to about 50 mg once/day;
preferred, from about 10 to about 30 mg once/day;

Fluvoxamine: from about 20 to about 500 mg
once/day; preferred, from about 50 to about 300 mg once/day;

5 Paroxetine: from about 20 to about 50 mg
once/day; preferred, from about 20 to about 30 mg once/day.

Sertraline: from about 20 to about 500 mg
once/day; preferred, from about 50 to about 200 mg once/day;

10 In more general terms, one would create a
combination of the present invention by choosing a dosage of
first and second component compounds according to the spirit
of the above guideline.

15 The adjunctive therapy of the present invention is
carried out by administering a first component together with
the second component in any manner which provides effective
levels of the compounds in the body at the same time. All
of the compounds concerned are orally available and are
normally administered orally, and so oral administration of
the adjunctive combination is preferred. They may be
20 administered together, in a single dosage form, or may be
administered separately.

However, oral administration is not the only route
or even the only preferred route. For example, transdermal
administration may be very desirable for patients who are
25 forgetful or petulant about taking oral medicine. One of
the drugs may be administered by one route, such as oral,
and the others may be administered by the transdermal,
percutaneous, intravenous, intramuscular, intranasal or
intrarectal route, in particular circumstances. The route
30 of administration may be varied in any way, limited by the
physical properties of the drugs and the convenience of the
patient and the caregiver.

The adjunctive combination may be administered as
a single pharmaceutical composition, and so pharmaceutical
35 compositions incorporating both compounds are important
embodiments of the present invention. Such compositions may
take any physical form which is pharmaceutically acceptable,

-17-

but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

-18-

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, alginates and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the

-19-

stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments.

Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. This enteric formulation is described in U.S. Patent No. 5,508,276, herein incorporated by reference in its entirety.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in

-20-

contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	25 mg
Fluoxetine, racemic, hydrochloride	20
Starch, dried	150
Magnesium stearate	<u>10</u>
Total	210 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	10
Fluoxetine, racemic, hydrochloride	10
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	<u>5</u>
Total	310 mg

The components are blended and compressed to form tablets each weighing 465 mg.

-21-

Formulation 3

An aerosol solution is prepared containing the following components:

	<u>Weight</u>
5	
Risperidone	5 mg
(+)-Duloxetine, hydrochloride	10
Ethanol	25.75
Propellant 22	
10 (Chlorodifluoromethane)	<u>60.00</u>
Total	100.75 mg

15 The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

20 Formulation 4

Tablets, each containing 80 mg of active ingredient, are made as follows:

	Sertindole	60 mg
25	(+)-Duloxetine, hydrochloride	20 mg
	Starch	30 mg
	Microcrystalline cellulose	20 mg
	Polyvinylpyrrolidone	
	(as 10% solution in water)	4 mg
30	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1 mg</u>
	Total	140 mg

35 The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinyl-

-22-

pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

10

Formulation 5

Capsules, each containing 130 mg of active ingredient, are made as follows:

	Quetiapine	70 mg
15	Fluoxetine, racemic, hydrochloride	30 mg
	Starch	39 mg
	Microcrystalline cellulose	39 mg
	Magnesium stearate	<u>2 mg</u>
	Total	180 mg

20

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

25

Formulation 6

Suppositories, each containing 45 mg of active ingredient, are made as follows:

30	Ziprasidone	75 mg
	(+)-Duloxetine, hydrochloride	5 mg
	Saturated fatty acid glycerides	<u>2,000 mg</u>
	Total	2,080 mg

35

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat

-23-

necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

5 Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

	Olanzapine	20 mg
	Sertraline	100 mg
10	Sodium carboxymethyl cellulose	
	50 mg	
	Syrup	1.25 ml
	Benzoic acid solution	0.10 ml
	Flavor	q.v.
15	Color	q.v.
	Purified water to total	5 ml

20 The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

25 Formulation 8

 An intravenous formulation may be prepared as follows:

	Olanzapine	20 mg
30	Paroxetine	25 mg
	Isotonic saline	1,000 ml

Benefit of the Invention

35 The present invention provides the advantage of treatment of psychotic conditions and mild anxiety with the atypical antipsychotics without the concomitant weight gain typically observed with such treatment, conferring a marked

-24-

and unexpected benefit on the patient. The present invention furthermore provides a potentiation of the increase in the concentration of norepinephrine observed as an effect of administration of a first component compound, by administration of a second component compound.

The present invention is particularly suited for use in the treatment of bipolar disorders, mania (mixed state), schizoaffective disorders characterized by the occurrence of a depressive episode during the period of illness, and depression with psychotic features. Such disorders may often be resistant to treatment with an antipsychotic alone.

The present invention also is useful for the treatment of premenstrual syndrome (PMS) and anorexia nervosa. Furthermore, the present invention is useful for the treatment of the aggression/violence which may be associated with certain disorders. These disorders include, but are not limited to, mania, schizophrenia, schizoaffective disorders, substance abuse, head injury, and mental retardation.

Psychotic conditions to be treated by the present method of adjunctive therapy include schizophrenia, schizophreniform diseases, acute mania, schizoaffective disorders, and depression with psychotic features. The titles given these conditions represent multiple disease states. The following list illustrates a number of these disease states, many of which are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM). The DSM code numbers for these disease states are supplied below, when available, for the convenience of the reader.

Paranoid Type Schizophrenia 295.30

Disorganized Type Schizophrenia 295.10

Catatonic Type Schizophrenia 295.20

Undifferentiated Type Schizophrenia 295.90

-25-

Residual Type Schizophrenia 295.60

Schizophreniform Disorder 295.40

Schizoaffective Disorder 295.70

Schizoaffective Disorder of the Depressive Type

5 Major Depressive Disorder with Psychotic Features 296.24,
296.34

Psychoses are often associated with other diseases and conditions, or caused by such other conditions. For example, they are associated with neurological conditions,
10 endocrine conditions, metabolic conditions, fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with central nervous system involvement. Psychoses may also be associated with use or abuse of certain substances. These substances include, but
15 are not limited to cocaine, methylphenidate, dexamethasone, amphetamine and related substances, cannabis, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics and anxiolytics. Psychotic disorders may also occur in association with withdrawal from certain substances. These
20 substances include, but are not limited to, sedatives, hypnotics and anxiolytics. The embodiments of the present invention are useful for treatment of psychotic conditions associated with any of these conditions.

25 Microdialysis assays of monoamines

Sprague-Dawley rats (Harlan or Charles River) weighing 270-300 grams are surgically implanted with microdialysis probes under chloral hydrate/pentobarbital anesthesia (170 and 36 mg/kg i.p. in 30% propylene glycol,
30 14% ethanol) (Perry and Fuller, Effect of fluoxetine on serotonin and dopamine concentration in rat hypothalamus after administration of fluoxetine plus L-5-hydroxytryptophan, Life Sci., 50, 1683-90 (1992)). A David Kopf stereotaxic instrument is used to implant the probe
35 unilaterally in the hypothalamus at coordinates rostral -1.5 mm, lateral -1.3 mm, and ventral -9.0 mm (Paxinos and Watson, 1986). After a 48 hour recovery period, rats are

-26-

placed in a large plastic bowl with a mounted liquid swivel system (CMA/120 system for freely moving animals, Bioanalytical Systems, West Lafayette, IN). Filtered artificial cerebrospinal fluid (CSF) (150 mM NaCl, 3.0 mM KCl, 1.7 mM CaCl₂, and 0.9 mM MgCl₂) is perfused through the probe at a rate of 1.0 ml/min. The output dialysate line is fitted to a tenport HPLC valve with a 20 µl loop. At the end of each 30 minute sampling period, dialysate collected in the loop is injected on an analytical column (Spherisorb 3 µ ODS2, 2X150 mm, Keystone Scientific).

The method used to measure monoamines is as described by Perry and Fuller (1992). Briefly, dialysate collected in the 20 µl loop is assayed for 5-HT, NE and DA. The 20 µl injection goes onto the column with a mobile phase which resolves NE, DA, and 5-HT: 75 mM potassium acetate, 0.5 mM ethylenediaminetetraacetic acid, 1.4 mM sodium octanesulfonic acid and 8% methanol, pH 4.9. The mobile phase for the amine column is delivered with a flow programmable pump at an initial flow rate of 0.2 ml/min increasing to 0.3 ml/min at 5 min then decreasing back to 0.2 ml/min at 26 min with a total run time of 30 min. Flow programming is used to elute the 5-HT within a 25 min time period. The electrochemical detector (EG&G, Model 400) for the amine column is set at a potential of 400 mV and a sensitivity of 0.2 nA/V. Basal levels are measured for at least 90 minutes prior to drug administration. The drugs are prepared in filtered deionized water (volume 0.25-0.3 ml) for administration at the desired doses.

-27-

We claim:

5 1. A method for treating a patient suffering from
or susceptible to psychosis, acute mania, mild anxiety
states, or depression in combination with psychotic
episodes, comprising administering to said patient an
effective amount of a first component which is an atypical
antipsychotic, in combination with an effective amount of a
10 second component which is a serotonin reuptake inhibitor.

 2. A method of **Claim 1** where the first component
is chosen from the group consisting of olanzapine,
clozapine, risperidone, sertindole, quetiapine, and
15 ziprasidone; and the second component is selected from the
group consisting of fluoxetine, venlafaxine, citalopram,
fluvoxamine, paroxetine, sertraline, milnacipran and
duloxetine.

20 3. A method of **Claim 1** wherein the first
component compound is olanzapine.

 4. A method of either of **Claims 1 or 2** wherein
the second component compound is fluoxetine.

25 5. A method of any of **Claims 1, 2, 3, or 4** where
administration of the compounds is oral.

 6. A method of **Claim 1** wherein the patient is
30 suffering from schizophrenia.

 7. A method of **Claim 1** wherein the patient is
suffering from a schizoaffective disorder.

35 8. A pharmaceutical composition which comprises a
first component which is an atypical antipsychotic, and a
second component which is a serotonin reuptake inhibitor.

-28-

9. A composition of **Claim 8** which comprises a first component chosen from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone, in combination with a second component chosen from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine.

10. A composition of **Claim 8** which is adapted for oral administration.

11. A composition of any of **Claims 8, 9, or 10** wherein the first component compound is olanzapine.

12. A composition of **Claim 11** wherein the first component compound is Form II olanzapine.

13. A composition of any of **Claims 8, 9, 10, 11, or 12** wherein the second component compound is fluoxetine or duloxetine.

14. A composition of **Claim 10** wherein the first component compound is olanzapine in the amount of about 0.25 to about 50 mg.

15. A composition of **Claim 10** wherein the first component compound is olanzapine in the amount of about 1 to about 30 mg.

16. A composition of **Claim 10** wherein the first component compound is olanzapine in the amount of about 1 to about 25 mg.

17. A composition of **Claim 10** wherein the second component compound is fluoxetine in the amount of about 10 to about 40 mg.

-29-

18. A composition of **Claim 10** wherein the second component compound is fluoxetine in the amount of about 20 to about 80 mg.

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15874

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55, 31/135

US CL :514/220, 651

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/220, 651

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS AND CAS ONLINE: compounds of the claims with psycho?, mani?, anxiet?, depressi?, schizo?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol. 124, 1995 (Columbus, OH), the abstract No. 76355, BAKSHI, V.P. 'Antagonism of Phencyclidine-Induced Deficits in Prepulse Inhibition by the Putative Atypical Antipsychotic Olanzapine.' Psychopharmacology 1995, 122(2), 198-201.	1-18
Y	BEASLEY, JR., C.M. Olanzapine Versus Placebo and Haloperidol: Acute Phase Results of the North American Double-Blind Olanzapine Trial. Neuropsychopharmacology. 1996, Vol.14, No.2, pages 111-123, especially page 122.	1-18
Y	BUDAVARI, Susan. The Merck Index, Eleventh Edition. Rahway, New Jersey: Merck & Co., Inc. 1989, page 655, entry no. 4112.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 13 NOVEMBER 1997	Date of mailing of the international search report 12 DEC 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KIMBERLY JORDAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)